. PYREXIA OF UNKNOWN ORIGIN

PREPARED BY :
DR RAFAT. H. LUBBAD

INTRODUCTION

- Body temperature is normally maintained within 1-1.5° c in a range of 37-38° c ,normal body temperature is generally considered to be 37°c . Low levels occur at 6 A.M and higher levels at 4 - 6 P.M
- 3. • Normal body temperature is maintained by a complex regulatory system in the anterior hypothalamus, preoptic area, temperature sensitive area, thermal set point .

PATHOGENESIS OF FEVER

. PYROGENS :

Substances mediate the elevation of core body temperature. Exogenous and endogenous pyrogens.

- Exogenous pyrogens: Derived from outside the host ,like Microorganisms, toxins and microbial products, large molecule ,can not pass blood brain barrier It induce release of endogenous pyrogens from macrophages.
- Endogenous pyrogens derived from the macrophages ,small molecule ,can pass blood brain barrier. •Pyrogen cytokines trigger hypothalamus to release PGE2 resulting in resetting of thermostatic temperature, activation of vasomotor center ,vasodilatation and heat production.

DEFINITION

- The definition of FUO derived by Petersdorf and Beeson in 1961 from a prospective analysis of 100 cases has long been the clinical standard :
- ●Fever higher than 38.3ºC on several occasions
- ●Duration of fever for at least three weeks
- ●Uncertain diagnosis after one week of study in the hospital

- ***DEFINITION EXPANSION:***
- 1. Classical PUO
- 2. Nosocomial PUO
- 3. Neutropenic PUO
- 4. HIV-Associated
- 5. Transplant

ESTABLISHING THAT A PATIENT HAS AN FUO

- The degree and duration of fever are not the only criteria for de
- fining an FUO. Prior to concluding that a patient has an FUO,
- the following evaluation should have been performed and should have been unrevealing:

- ●History

- ●Physical examination

- Complete blood count, including differential and platelet count

- ●Blood cultures (three sets drawn from different sites with an interval of at least several hours between each set; in cases in which antibiotics are indicated, all blood cultures should be obtained before administering antibiotics)

- ●Routine blood chemistries, including liver enzymes and bilirubin

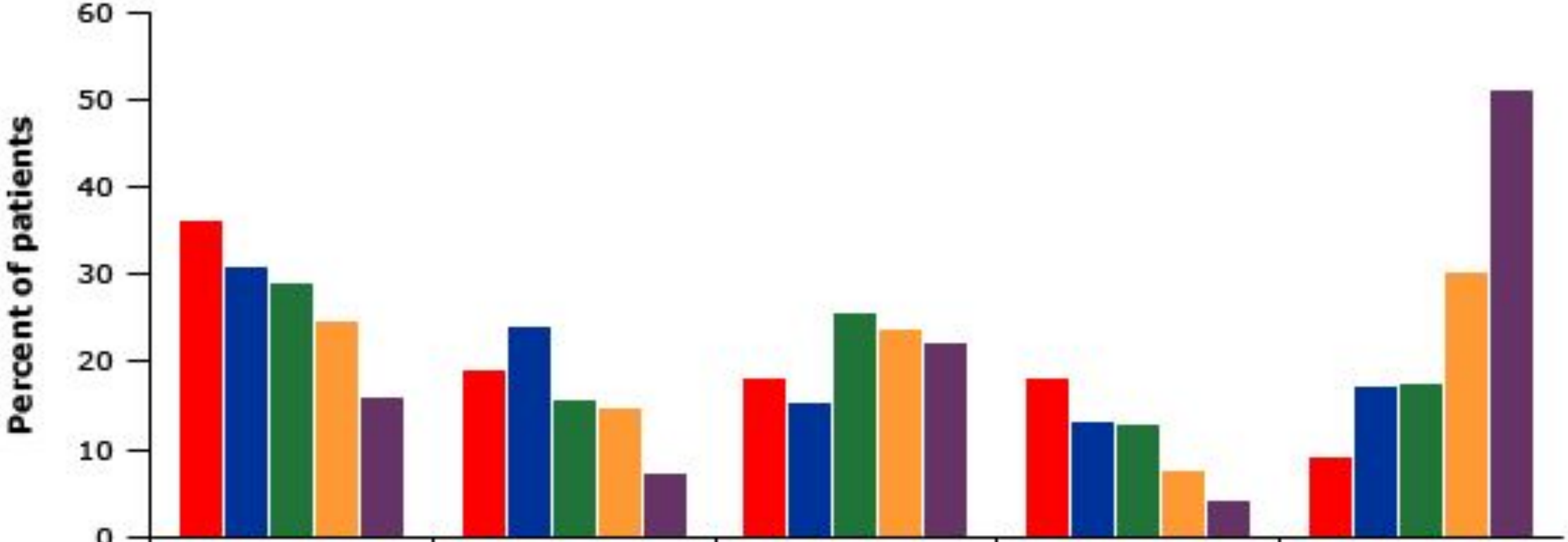
- ●If liver tests are abnormal, hepatitis A, B, and C serologies

- ●Urinalysis, including microscopic examination, and urine culture

- ●Chest radiograph

ETIOLOGY:

- Three general categories of illness account for the majority of "classic" FUO cases and have been consistent through the decades. These categories are:
- ●Infections
- ●Malignancies
- ●Systemic rheumatic diseases (eg, vasculitis, rheumatoid arthritis)



	Infection	Malignancy	Inflammatory	Other	No Diagnosis
1950s	36	19	18	18	9
1970s	30.8	23.9	15.1	13	17.2
1980s	29	15.6	25.4	12.7	17.3
1990s	24.5	14.5	23.5	7.5	30
2000s	16	7	22	4	51

- **True FUOs are uncommon:**

- The following distribution of causes was noted:

- ●Systemic rheumatic disease (eg, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica) – 22 percent

- ●Infection – 16 percent

- ●Malignancy – 7 percent

- ●Miscellaneous – 4 percent

- ●No diagnosis – 51 percent

NOSOCOMIAL PUO

- . Temperature >38.3°C Patient hospitalized ≥ 24 hours but no fever or incubating on admission , Evaluation of at least 3 days
- • More than 50% of patients with nosocomial PUO are due to infection.
- • Focus on sites where occult infections may be sequestered, such as: - Sinusitis of patients with NG or Oro-tracheal tubes. - Prostatic abscess in a man with a urinary catheter.
- • 25% of non-infectious cause includes: - Acalculous cholecystitis, - Deep vein thrombophlebitis - Pulmonary embolism.

IMMUNE DEFICIENT/ NEUTROPENIC PUO

- Temperature >38.3°C , Neutrophil count ≤ 500 per mm3
- Evaluation of at least 3 days
- • Patients on chemotherapy or immune deficiencies are susceptible to:
  - - Opportunistic bacterial infection
  - - Fungal infections such as candidiasis
  - - Infections involving catheters
  - - Perianal infections.
- • Examples of etiological agent: - aspergillus - Candida - CMV - Herpes simplex

HIV-ASSOCIATED PUO

- Temperature >38.3°C , Duration of >4 weeks for outpatients,& >3 days for inpatients , HIV infection confirmed
- • HIV infection alone may be a cause of fever.
- • Common secondary causes include: - Tuberculosis - CMV infection • Non-Hodgkin's lymphoma - Drug-induced fever

CLINICAL APPROACH PYREXIA OF UNKNOWN ORIGIN

- **History Taking (HOPI)** 。
- 1. Onset :- acute: , - gradual:
- 2。Character;
- 3。Antecedents : dental extraction: , Urinary catheterization;
- 4。 Associated symptoms : Chills & rigors , Night sweats , Loss of weight , Cough and Dyspnea , Headache , Joint pain

- . Abd. Pain , Bone pain , Sore-throat , Dysuria, rectal pain , Altered bowel habit , Skin rash
- PMH , PSH . DRUG-Hx , F/Hx
- Travel , Residential area , Occupation , Contact with domestic / wild animal / birds : Diet history , Sexual orientation , Close contact with TB patients

PHYSICAL EXAMINATION PYREXIA OF UNKNOWN ORIGIN

- GENERAL : HANDS ,ARMS , AXILLA , HEAD, , EYE , FACE , MOUTH
- Abdomen :T.FEVER , HMG , SMG , RCC , Testis , DRE , PV
- CHEST;CVS, RS , Signs of meningism ,

INVESTIGATION PYREXIA OF UNKNOWN ORIGIN

- Stage 1: Laboratory investigations Stage 1: (screening tests)
- 1. Full blood count
- 2. ESR & CRP
- 3. BU&SE
- 4. LFTs
- 5. Blood culture
- 6. Serum virology
- 7. Urinalysis and culture
- 8. Sputum culture and sensitivity
- 9. Stool occult blood
- 10. CXR
- 11. Tuberculin test

. Microscopy: Direct examination of b.smears

- Stage 2:
- 1. Repeat history and examination
- 2. Protein electrophoresis
- 3. CT (chest, abdomen, pelvis)
- 4. Autoantibody screen (ANA, RF, ANCA, anti- dsDNA)
- 5. ECG Stage 2: Laboratory investigations
- 6. Bone marrow examination
- 7. LP
- 8. Temporal artery biopsy
- 9. HIV test counselling

. Stage 3:

1. Echocardiography

2. (Indium-labelled WC scan – IBD, abscesses, local sepsis)

3. Barium studies

4. IVU

5. Liver biopsy

6. Exploratory laparotomy

7. Bronchoscopy

Imaging Studies Chest radiograph CT of abdomen or pelvis with contrast agent Gallium 67 scan MRI of brain PET scan Transthoracic or transesophageal echocardiography Venous Doppler study

Pyrexia of Unknown Origin:

- The majority of disease remaining after an initial NEGATIVE work-up are:
- 1. Neoplasm
- 2. Seronegative Collagen Vascular Disease
- 3. TB
- 4. Drug
- 5. Elderly with Endocarditis
- 6. HIV with or without infection or malignancy
- 7. Implanted prosthetic devices
- 8. Travel …

1. INFECTIVE ′

Localized pyogenic infection ′ Systemic bacterial eg typhoid ′ Mycobacterial MTB,MAI ′ Fungal e.g. cryptococcus, histoplasmosis ′ Viral e.g. HIV,CMV ′ Parasitic e.g. Malaria, Toxoplasmosis, babesiosis ′ Rickettsia .

2.NEOPLASMS ′

Lymphoma ′ Leukaemia ′ Liver, renal, colon, pancreatic ′ Sarcoma ′ Atrial myxomas

3. COLLAGEN VASCULAR DISEASES ′ Adult Still’s disease ′ SLE ′ RA ′ PAN ′ Wegeners Granulomatosis ′ Still’s Disease ′ Polymyalgia rheumatica ′ Rheumatic fever ′ Behcets

4.MISCELLANOUS ′ Granulomatous diseases i.e. Sarcoid, Crohn’s ′ Drug Induced Fever ′ Endocrine e.g. Thyrotoxicosis, Phaeocromocytoma ′ Intracerbral e.g. SOL, Pontine CVA ,Encephalitis ′ Metabolic / inherited e.g. Familial Mediterranean Fever ′ Tissue infarction e.g. post MI (Dressler's syndrome), recurrent Pulmonary Embolism ′ Factitious fever

5. ANTIBIOTICS: Erythromycin Isoniazid Nutrofurantoin Penicillin DRUGS CAUSING FEVER Others: Allopurinol Cimetedine Clifibrate Heparin Phenytoin Procainamide Quinidine Meperidine Antihypertensives: Captopril Hydralizine Hydrochlorothiazide Methyl Dopa Nifedepine

1. ETIOLOGIES OF PUO ′ Infection : Tuberculosis: Disseminated ′ The single most common infection in most PUO series except in children ′ Usually extrapulmonary or miliary ′ Occurs in the lungs when significant pre-existing lung disease. ′ Pul. TB in AIDS is often subtle (normal CXR in 15 – 30%). ′ PPD is +ve < 50% of TB with PUO. ′ Diagnosis often requires biopsy of LN/Liver/Bone marrow.

- ETIOLOGIES OF PUO ′ Abscess: : Usually located in abdomen or pelvis. • Secondary to appendicitis or diverticulitis. • Pyogenic liver abscess usually follow biliary tract disease or abdominal suppuration • Amoebic liver abscess is similar to pyogenic → amoebic serology is positive > 95% of cases.(IHA,ELISA) • Splenic abscess is usually secondary to hematogenous seeding. • Perinephric or renal abscess is usually secondary to UTI.

- ETIOLOGIES OF PUO ′ Bacterial Endocarditis • Culture remains negative in 5% of patient. • Culture negative is likely with the following organisms: ′ Coxiella burnetii → no growth. ′ HACEK group → incubate blood 7 – 21 days, slow growing ′ Brucella } Special media ′ Legionella Long Time ′ Mycoplasma/Chlamydia ′ Fungal → usually sterile • Peripheral signs may not be detected.
- Right-side endocarditis lack murmurs

ETIOLOGIES OF PUO ′ MALIGNANCY • Lymphoma: Fever is a presenting feature • Leukemia: M. Myeloma (fever means infection) • Renal cell carcinoma: only rarely fever is there • HCC or secondary metastasis to the liver

Lymphoma: • Fever is a well-recognized manifestation. • A Pel-Ebstein phenomenon is rare. • Source of fever : production of cytokines. • Fever is a negative prognostic factor ′ Renal Cell Carcinoma (Adult) • 20% present with fever • Microscopic hematuria

- ETIOLOGIES OF PUO ′ Wilms Tumor (Children) • Peak incidence 2-3 years. • Abdominal mass but FEVER can be a presentation. ′ Solid Tumor • Fever is rare except: ′ Secondary metastasis to the liver ′ Ductal obstruction or perforation like cholangioacarcinoma or ampulla carcinoma ′ Lung carcinoma with obstruction and pneumonia.

COLLAGEN-VASCULAR-DISEASE No diagnostic serology The syndrome needs to be identified for diagnosis • Still's disease (young or adult) • Giant cell arteritis } → 15% of PUO • Polymyalgia Rheumatica } • Behcet's Disease • Relapsing polychondritis

′ Adult Onset Still's Disease ′ Age 16 – 35 with (-ve) RF & ANA • Fever is high and spiking with temp. up to 41.6oC (hectic) • Fever is either intermittent or remittent (peaks typically at night) • Most patient seek medical attention within 2 weeks. • A distinctive evanescent macular or papular rash is typically present during the course of the illness. • Dx is strictly a clinical: RF is almost uniformly negative. • Other features: myalgias, arthritis, leukocytosis (neutrophils), hepatosplenomegaly & lymphadenopathy. • high serum ferritin (> 2000)

TEMPORAL ARTERITIS: • Very serious condition if not diagnosed early • Very difficult to establish the etiology of fever without high index of suspicion • Fever and malaise may be the only manifestation. Headache is the most common. • Common cause of puo in elderly >70 yrs • Tenderness or decreased pulsation guide the selection of site of bx • “blind biopsy” of one or both temporal arteries may yield to diagnosis

POLYMYALGIA RHEUMATICA: • Can cause fever, arthralgia, myalgia & ↑ ESR > 50. • Characteristic muscle complaints: symmetrical pain and stiffness that are typically worse at morning • Affects lumbar spine and large proximal muscles ′ Other vasculitides that cause PUO: • Polyarteritis nodosa → Mononeuritis multiplex (60%) • Wegener’s Granulomatosis • Mixed Cryoglobulinemia

MISCELLANEOUS CAUSES: (Non-Infectious) • Vascular Causes: ′ Pulmonary Emboli ′ 50% are febrile ′ Fever is characteristic (< 39oC) ′ Patient typically has predisposing factors : cancer or recent immobility. ′ Hematoma in closed space ′ Hemorrhage in the retroperitoneal space ′ Within the wall of an aneurysm or dissection of the thoracic or abdominal aorta.
FACTITIOUS FEVER In a study 9% of cases of PUO were factitious • False fever: ′ Thermometer manipulation using external heat or substitute thermometer. • Genuine fever (self induced) ′ Administration of pyrogenic substances (bacterial suspensions) ′ Generally young women with connection to health care often NURSES.

It is axiomatic that as the duration of fever increases, the likelihood of an infectious cause decreases even for the more indolent infections (brucellosis, paracoccidiomycosis, etc.)
PYREXIA OF UNKNOWN ORIGIN The majority of disease remaining after an initial NEGATIVE workup are: 1. Neoplasm 2. Seronegative collagen vascular disease 3. Progressive Tuberculosis 4. Increasing Drug Addition 5. Elderly with Endocarditis 6. HIV with or without infection or malignancy 7. Prosthetic devices / implants 8. Travel

CLINICAL ′ History ′ Travel: • Travel to an area known to be endemic for certain disease: Name of the area, duration of stay Onset of illness (incubation period) 1 – 10 Days 10 – 21 Days Weeks - Months Malaria Malaria Kala Azar Plague Typhoid Amoebiasis Dengue Brucella HIV Salmonella Hepatitis A

- PHYSICAL EXAMINATION ′ Localizing Symptoms may Indicate the source of fever: Back Pain TB Spondylitis Bone Metastasis Headache Chronic Meningitis/GCA RUQ Pain Liver Abscess LUQ Pain Splenic Abscess Oral & Genital Ulcer Behcet’s Disease Jaw Claudication Temporal Arteritis Subtle changes in behavior Granulomatous Meningitis .

ROLE OF LAB INVESTIGATIONS MINIMAL DIAGNOSTIC CRITERIA ′ History & Physical examination ′ CBC & DLC, TLC ′ U/A and Microscopy ′ Chest X-ray ′ Blood Cultures x 3 ′ Urine culture ′ LFTs ′ Hepatitis serologies (if abnormal LFTs) ′ Chem10 OTHER TESTS ′ ESR/CRP ′ Peripheral Smear ′ Anti Nuclear Antibody ′ Rheumatoid Factor ′ HIV ′ CMV IgM ′ Mono Spot ′ PPD

Complete Blood Count • Anemia suggests a serious underlying disease • Leukocytosis with bands → occult bacterial infection • Lymphocytosis & atypical lymphocyte → Infectious mononucleosis • Leucopenia and lymphopenia → advanced HIV, typhoid • Leukoerythroblastic Anemia → Disseminated TB • Thrombocytopenia → Malaria/Leukemia • Peripheral Blood → Malaria and other parasites
CRITICAL EVALUATION ROUTINE
ROUTINE • ESR & CRP is elevated in: 1. Bacterial Infection 2. Neoplasm 3. Immunological-mediated inflammatory states 4. Tissue infarction 58%: malignancy like Lymphoma/myeloma 25% Infection: Endocarditis, Giant cell arteritis
ROUTINE • ↑ High ESR → lacks specificity: ′ Drug Reaction ′ Thrombophlebitis may cause very high ESR ′ Nephrotic Syndrome • Normal ESR → significant inflammatory process is absent with exception. ′ CRP-level may be useful cross reference for ESR ′ More

MARKERS OF INFLAMMATION ′ Acute Phase Proteins Proteins Increased Proteins Decreased Fibronogen Albumin Ferritin Transferrin Plasminogen Fetoprotein Protein S Ceruloplasmin LAB EVALUATION ′ Blood Testing • Anti-nuclear Antibodies • Rheumatoid Factor • CMV Antibody: IgM • Heterophile Antibody Test in children and young adult • Thyroid Function Test • HIV Screening • Angiotensin converting enzyme • Febrile agglutinins LAB EVALUATION ′ Cultures • Blood ′ Obtain more than 3 blood cultures from separate sites over 24 hr period prior to antibiotics if Infective Endocarditis is suspected ′ Lysis centrifugation blood culture techniques • Sputum: For Tuberculosis • Any normal sterile: CSF/urine/pleural or peritoneal fluid • Bone marrow aspirate → Tuberculosis/Brucellosis • Lymph node aspirate → TB

Hepatomegaly or Abnormal LFT ′ Hepatic Granuloma ′ Non-caseating: Tuberculosis/Sarcoidosis & Brucellosis ′ Caseating: Tuberculosis • Bone Marrow ′ Granuloma ± Tubercle Bacilli → Tuberculosis ′ Aplastic Cells → Leukemia ′ Leishmania Bodies → Kala-Azar ′ Atypical Cells → Lymphoma ′ Atypical Plasma Cells → Multiple myeloma • Pleural or pericardial fluid→ Extrapulmonary Tuberculosis • Temporal artery biopsy→ Giant Cell Arteritis LAB EVALUATION - BIOPSY

OTHER INVESTIGATION ′ IMAGING STUDIES:
to localize abnormalities for definite tests or treatment • Chest x-ray: ′ Miliary shadows → disseminated tuberculosis ′ Atelectasis ′ ↑ Hemi diaphragm ′ Pleural Effusion ′ Mediastinal mass → Lymphoma/Tuberculosis/ Sarcoid ′ If CXR is WNL → Repeat on weekly basis • Ultra sonography Hepatic, Splenic, Pancreatic or Subphrenic Abscess

IMAGING STUDIES • CT-SCAN → CT scan chest ′ Mediastinal mass → Tuberculosis/Lymphoma/ Sarcoidosis ′ Dorsal Spine → Spondylitis and disc space disease ′ CT-Scan Abdomen → very effective to visualize ′ All types of abscesses ′ Retroperitoneal tumor, lymph node or haematoma • MRI: spleen, lymph node and the brainRadionuclear Scanning Bone TC-scan → osteomyelitis (skeletal),bony metastasis GALLIUM SCAN → occult inflammation, pneumocystis Indium labeled WBC-scan → occult abscesses FLUORODEOXYGLUCOSE F18(FDG)PET SCANNING appears to be superior to other forms of nuclear imaging FDG USED IN PET scans accumulates in tumour and at sites of inflammation NEWER TECHNIQUES

GALLIUM SCAN ′ Will be hot if there is: • Increased blood flow • Uptake by bacteria (lactoferrin) • Uptake by WBC ′ Sensitive but not specific ′ Not recommended for abdomen or pelvis: false +ves are common ′ Effective in: • Chronic Infection • Lymphoma INDIUM-LABELED LEUKOCYTE ′ Uptake by WBC ′ Only for acute problem (less than 4 weeks) ′ Study in the UK has found the sensitivity for infective PUO: 25% and specificity was 100% ′ Recommended for strongly suspected infective PUO if done within the 1st 2-4 weeks ′ False positive: post op wound, mastitis Retroperitoneal angiosarcoma demonstrating mild uptake of In111-WBC.

- LAPAROSCOPY • To visualize and biopsy the pathology in the abdomen e.g. Tuberculous peritonitis Peritoneal carcinomatosis ′ Biopsy • Enlarged lymph node ′ Granulomatous disease (Tuberculosis) ′ Others ′ Metastatic carcinoma HISTOPATHOLOGICAL EVALUATION Lymph node biopsy showing tumor cells, which have either vacuolated or pale mucin filled cytoplasm. Many signet ring cells are seen and occasional mitoses are present. Also seen are tiny pools of mucin along with the tumor cells. Normal lymph node tissue is seen at the right upper corner

SUMMARY :

The most important aspects of the evaluation of a patient with FUO are to take a careful history, perform a detailed physical examination, and to reassess the patient frequently. × Diagnostic workup may fail to identify an etiology in as many as 30 to 50 percent of patients. × Most adults who remain undiagnosed have a good prognosis.

THAK YOU